In a third related method, the invention features a method of conditionally ablating a cell lineage, the method involving: (a) providing a first transgenic non-human mammal which includes an activator protein expressed only in the cell lineage; (b) providing a second transgenic non-human mammal which includes a nucleic acid sequence encoding a cell ablation factor, the nucleic acid sequence being under the control of the activator protein and the activator protein being capable of binding to and regulating the nucleic acid sequence only upon induction; (c) mating the first and the second transgenic mammals to produce offspring in which the cell ablation factor is expressed under the control of the activator protein, the cell ablation factor being capable of destroying cells in which it is expressed; and (d) inducing binding and regulation by the activator protein.

In preferred embodiments, the activator protein is introduced into the transgenic non-human mammal on a retroviral vector that includes a splice acceptor sequence, a transcription termination sequence, and retroviral packaging and integration sequences; the activator protein is a tetracycline repressor fused to VP16 and the nucleic acid sequence encoding a cell ablation factor is operably linked to a tetracycline operator; the cell ablation factor is chosen from the group consisting of a toxin, a thymidine kinase, or an apoptotic protein; the conditional induction occurs by administration of tetracycline or a tetracycline derivative to the transgenic mammal; and the mammal is a mouse.

In a fourth related method, the invention features a method for conditional ectopic expression of a gene of interest, the method involving: (a) providing a first transgenic non-human mammal which includes an activator protein expressed under the control of the promoter of an endogenous gene of the mammal; (b) providing a second transgenic non-human mammal which includes a nucleic acid sequence encoding the gene of interest, the nucleic acid sequence being under the control of the activator protein and the activator protein being capable of binding to and regulating the nucleic acid sequence only upon induction; (c) mating the first and the second transgenic mammals to produce offspring in which the gene of interest is expressed under the control of the activator

protein; and (d) inducing expression of the activator protein.

In preferred embodiments, the activator protein is introduced into the transgenic non-human mammal on a retroviral vector that includes a splice acceptor sequence, a transcription termination sequence, and retroviral packaging and integration sequences; the activator protein is a tetracycline repressor fused to VP16 and the nucleic acid sequence encoding a cell ablation factor is operably linked to a tetracycline operator; the induction occurs by administration of tetracycline or a tetracycline derivative to the transgenic mammal; and the mammal is a mouse.

In a fifth related method, the invention features a method of generating a non-human transgenic mammal having a conditional malignancy, the method involving: (a) providing a first transgenic non-human mammal which includes an activator protein expressed under the control of the promoter of an endogenous gene of the mammal; (b) providing a second transgenic non-human mammal which includes a nucleic acid sequence encoding a neoplastic factor, the nucleic acid sequence being under the control of the activator protein and the activator protein being capable of binding to and regulating the nucleic acid sequence only upon induction; (c) mating the first and the second transgenic mammals to produce offspring in which the neoplastic factor is expressed under the control of the activator protein, the neoplastic factor being capable of promoting the development of the malignancy; and (d) inducing binding and regulation by the activator protein.

In preferred embodiments, the activator protein is introduced into the transgenic non-human mammal on a retroviral vector that includes a splice acceptor sequence, a transcription termination sequence, and retroviral packaging and integration sequences; the activator protein is a tetracycline repressor fused to VP16 and the nucleic acid sequence encoding a cell ablation factor is operably linked to a tetracycline operator; the neoplastic factor is an oncogene; the induction occurs by administration of tetracycline or a tetracycline derivative to the transgenic mammal; and the mammal is a mouse.

The invention also features a cell line derived from one of these transgenic non-human mammals, as well as transgenic mosaic non-human mammals generated by the methods of the invention and uses therefor.

In a final related method, the invention features a method for conditional tissue-specific inactivation of a gene of interest, the method involving: (a) providing a first transgenic non-human mammal which includes an activator protein expressed under the control of the promoter of the endogenous gene of interest; (b) providing a second transgenic non-human mammal which includes a ribozyme gene under the control of the activator protein, the ribozyme being capable of specifically interfering with expression of the gene of interest and the ribozyme being produced only upon induction; (c) mating the first and the second transgenic mammals to produce offspring in which the ribozyme is expressed under the control of the activator protein; and (d) inducing expression of the activator protein, whereby the gene of interest is inactivated in cells in which it is endogenously expressed.

In preferred embodiments, the activator protein is introduced into the transgenic non-human mammal on a retroviral vector that includes a splice acceptor sequence, a transcription termination sequence, and retroviral packaging and integration sequences; the activator protein is a tetracycline repressor fused to VP16 and the nucleic acid sequence encoding a ribozyme is operably linked to a tetracycline operator; induction occurs by administration of tetracycline or a tetracycline derivative to the transgenic mammal; and the mammal is a mouse.

The present invention provides a number of advantages. For example, it combines versatile retroviral vectors for ES cell mutagenesis with powerful detection methods for rapid identification of mutant cells of interest. In addition, the method permits mutagenesis in a large number of mammalian genes, in a short period of time, and at a significant reduction in cost. Moreover, the method may be readily streamlined, and